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ADVANCES IN SYNTHETIC DRUGS FOR SCHISTOMIASIS

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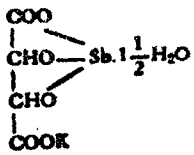
ADVANCES IN SYNTHETIC DRUGS FOR SCHISTOSOMIASIS

/The following is a full translation of an article by CHI Ju-yun, of the Drug Research Institute, Chinese Academy of Sciences, published in K'o-hsueh T'ung-pao (Scienta), No.3, Peiping, 11 March 1960, pages 133-135./

Schistosomiasis is a parasitic disease of considerably high incidence on a world wide scope. There are many kinds of the disease. In Africa and South Africa, An's schistosomiasis and Egyptian schistosomiasis are prevalent. In China what is prevalent is Japanese schistosomiasis. Different types of schistosomiasis appear to react differently to drugs. For many years the drug principally used has been antimony potassium tartrate. (I)



I. antimony potassium tartrate

This drug has been found definitely efficacious in the treatment of all the three kinds of schistosomiasis mentioned above.

The defect is that it must be administered through injection into the veins, and there are many reactions, including occasional cases of poisoning.

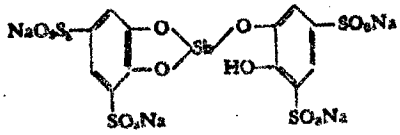
The decades various countries in the world have been continually seeking new drugs for schistosomiasis. In recent years in China we have compouned and experimented on many drugs and among them we have discovered several efeective drugs.

Antimony compounds. Different types of antimony compounds often have curative effects to varying extent on schistosomiasis. But antimony is a poisonous substance, and the problem is the production of compounds with lower poisonous content. Certain organic substances, mixed with antimony, produce a stabilized compound which dissolves gradually inside the body, and as inorganic antimony has a very low degree of concentration, the poison is not great.

Antimony potassium tartrate is the compound produced from hydroxy acid, tartrate and antimony. Other kinds of hydroxy acid may also be mixed with antimony to produce a similar compound. We have found that antimony ammonium gluconate(1) has a lower poisonous content than antimony potassium tartrate. When a dosage of the former of two to three times that of the latter is used, the reaction is about the same, but the curative value is higher. The defect of this new drug is that the liquid is not stabilized and sedimentation easily occurs. In experiments carried out on animals, the simple compound of hydroxy acid, glyceryl acid salt and antimony has also been found more effective than antimony potassium

tartrate when injected into the veins, but the effects from oral application have not been satisfactory.

Phenol compounds are hydroxy derivatives of the aromatic species. This hydroxy is more acid than the hydroxy of compounds of the fatty species. It can therefore be easier mixed with antimony to form phenolates. Fuadin is the antimony deriative from sodium phenol disulfonic, and this has also been placed under clinical tests in foreign countries. The good point is that it can be administered through injection into the muscles. Clinical tests carried out in China show that it is not as effective as antimony potassium tartrate. If higher concentration is used, the results may be better. but reaction in the intestines is more marked compared with the use of antimony potassium tartrate.



II. Fuadin

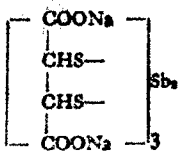
Sulphur is matter "with the same electricty content but with a different element" from oxygen. Sulfide compounds belong to the same class as hydroxy compounds, but theformer are more acid than the latter, and so more easily turn into thio-alcohol salt. Disulfide compounds with antimony produce cyclo-thio-alcohol salt, and its chemical state is more stable than the antimongy-sulphur

thio-alcohohol salt from simple sulfide compounds. It cannot be easily disintegrated and so the poisonous content is lower.

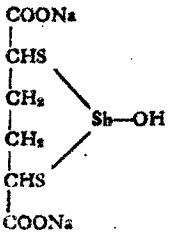
Disulfide propyl alcohol (BAL) and disulfide propionic acid (YHATHON) are both metal anti-toxic agents, but their curative value applied to Japanese schistosomiasis is not as high as antimony potassium tartrate. Disulfide succinic acid socium is an antimony anti-toxic found in China, and its anti-toxic effects are much better than those of disulfide propyl alcohol.(2) The cyclo antimony sulphur thio-alcohol salt of this anti-toxic is disulfide succinic acid antimony sodium (Sb-58), and its chemical structure is similar to the TWSb manufactured by Friedheim.(3) It has undergone thousands of clinical tests in Shanghai, Anhwei, Chekiang, and Kiangsu.(4) The good points are that it can be injected into the muscles, reaction is less marked than that to antimony potassium tartrate, and when applied to short term cure, the efficacy is not lower than that of antimony potassium tartrate. It can be used on patients in the later stages of the disease. Used for the cure of draft cattle suffering from schistosomiasis, the results have also been satisfactory.

Disulfide butane dicarboxylic acid antimony sodium (Sb-126) is a cyclo antimony sulphur thio-alcohol salt of similar structure. In experiments on animals, the curative value is even better than Sb-58. Its rate of discharge is slower and when a dose half that of Sb-58 is given, the antimony content in the

blood is not less than that in the injection of Sb-58. Clinical tests are being conducted with this drug.

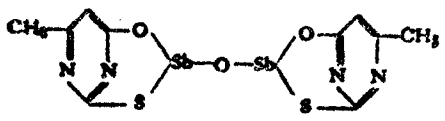


III Disulfide succinic acid antimony sodium (Sb-58)



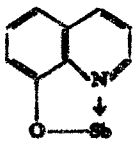
IV Disulfide butane dicarboxylic acid antimony sodium (Sb-126)

Methyl radical sulpha-oxygen pyrimidine is another antimony anti-toxic. It contains a sulphur radical and a hydroxy radical, and can also produce a cyclo antimony compound, oxide dimethyl sulpha-oxide pyrimidine antimony (V). In tests applied on animals with the oral application method, the worms were reduced by 99.8 percent, and cures reached 94 percent.(6) Clinical tests were very satisfactory, but the course of treatment is rather long (from seven to twenty days) and reaction in the intestines is very acute.



V. Oxide dimethyl sulpha-oxidepyrimidine antimony

Amino compounds may form with antimony complexes difficult of dissociation. Certain antimony complexes from alkaloids, compound drugs and dyestuffs yielded good curative results when experimented on animals. Among these, extensive clinical tests had been carried out with hydrochloric acid quinine antimony(7), and though there were definite results, reaction in the intestines was rather acute. 8-hydroxy quininic antimony, in addition to a cyclo-amino radical, has also a phenol hydroxy, and can form with antimony a cyclic prong like structure, with morestabilized chemical properties, and less poisonous than antimony potassium tartrate. In clinical tests, reaction was lighter. Treatment by the oral administration method over a period of 20 days in early stages of the disease resulted in 64 percent cures.(8)

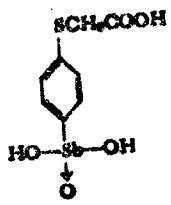


VI. 8-hydroxy quinninic antimony

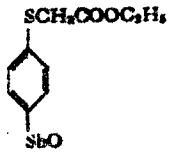
Para-carboxyl methyl hydrogen sulphide phenyl stibbins acid is a penta-valence compound, and of the molecules, antimony is compounded with carbon atom. Curative tests on rats, rabbits and monkeys yielded better results than antimony potassium tartrate,(9) and poison is less pronounced. However, long term

treatment (more than 14 days) is necessary, and in a short term (three-day) treatment of a domestic rabbit, the e was no marked result. (Sb-11, formula VII).

Phenyl-stibine compounds produced from the reduction of ethyl corresponding to that of Sb-11 have been found to have good curative values in experiments with animals and in clinical tests. High curative effects have also been found in corresponding phenyl-stibine compounds from substitute radical groups of certain phenyl para-compounds.



VII Para-carboxyl methyl hydrogen sulphide phenyl stibine acid

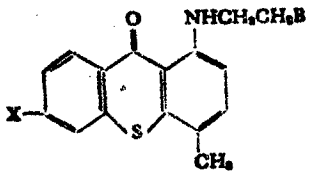


VIII Oxidized para-ethylene carbonic methyl hydrogen sulphide phenyl stibine

Because of the curative effects of antimony compounds for schistosomiasis, we have experimented on many other metal compounds. Certain corresponding compounds of tin have also been effective, but they are not as good as antimony agents.(11) Bismuth compounds have some curative value. Without curative value are organic deriatives of such metals as cadmium, iron, silver, lanthanum, molybdenum, zinc, nickel, copper, lead, cerium, gold,

tungsten, vandadium, aluminum, manganese, magnesium, cobalt and mercury.

Non-Antimony Compounds. After antimony agents had been in use for many years, in 1946 there was discovered outside China an effective non-antimony agent:
1-diethyl ethyl-4-methyl-10-sulphate hetero anthracene-9-ketones. (Lucanthone, Nilodin, Miracil-D).[12] (formula IX)



IX a, X = H, B = N $(C_2H_5)_2$ Miracil - D

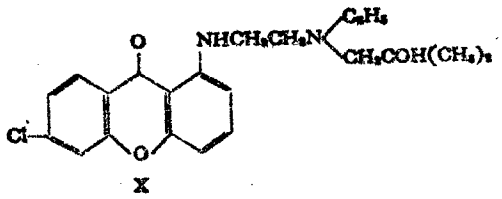
b, X = H, B = N $(C_4H_9)_2$

c, X = Cl, B = N (C_4H_9) $CH_2CHOHCH_3$

However, after several clinical tests, it was discovered that an effective dose brought with it too great by-effects, so that it was not practical, and it was not specially efficacious for Japanese schistosomiasis.[13] A few years later, Archer et al reported[14] that if diethyl was replaced by di-butyl amine (IXb), the curative index would be higher. And if on the amino, hydroxy is added to alkyl, the curative effect would be further increased, and poison would be reduced, so that the curative index would be increased by ten times over IX a.

In China, we have experimented with many kinds of similar

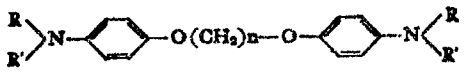
compounds with animals afflicted with Japanese schistosomiasis. We found IXa not effective at all, while IXc only could slightly reduce the growth of worms. Furthermore, Archer et al [14] also reported curative effects on Man's schistosomiasis by several drugs of para oxide hetero anthracene ketones, with a dosage of 25 milligram/kilogram (formula X), but there were no subsequent clinical rest reports.



X

In recent years, Raison and Standen [15] declared that superior effects in the treatment of schistosomiasis were derived from diamino diphenyl oxide alkyl compounds. In China these drugs were uased in clinical tests in a small number of cases, but it was unexpectedly discovered that the amount of poison was large and there was no curative effect.[16] The poison led principally to damage to eyesight, dimness, night blindness, blinking and color blindness. Outside the country there were at the same time reports on damage to eyesight.[17] The series of compounds were also tried on animals afflicted with Japanese schistosomiasis, and only heptane compounds

(formula XI, R, R' = H, n = 7) could destroy a small number of the worms.[18]



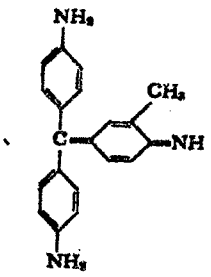
XI n = 5 - 8, R, R' = H, CH_3 or C_2H_5

In an attempt to change the relationship between the poison and the curative effect, Chang Chi-chieh and others [19] changed in part the chemical structure, and produced many relevant compounds. In tests made on animals[20] it was discovered that when the akyl radical R on the amino was changed into CH_2SO_3Na or CH_2SO_2Na, the poison would be reduced, but the effect was not reduced. If the carbon chain (CH_2) on the aromatic oxide was changed into $(CH_2)_2O(CH_2)_2$, the poison would be greatly reduced, but the effect would also be weakened. Though many compounds had been experimented upon, we could not find data that would recommend any drugs for clinical tests.

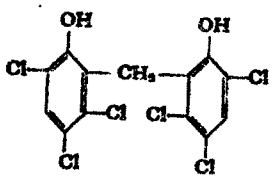
Apart from the above two categories of non-antimony compounds, Ting Kuang-sheng and others[21] also selected many dyestuffs, and among them discovered rosaniline, formula XII) and para rosaniline, which have both preventive and curative effects on white mice afflicted with Japanese schistosomiasis. The effects are even better than those two classes of compounds included in IX and XI. But the period of treatment is rather long, and discharge is very

slow. Reports from outside the country stated that the accumulation of the compounds inside the human body may lead to the incidence of cancer. So they have not been used in clinical tests.

In addition, in making selections among proprietary drugs, we also found definite curative effects from hexachlorophene, formula XIII).[22] However, this compound is a disinfectant for external use, with a high poison content. Only with a dose with a medium quantity of poison could half the grown worms be destroyed, and so it was also not suitable for clinical tests. It destroys female worms better than male worms.



XII Rosaniline



XIII Hexachlorophene

Some views on research on drugs for schistosomiasis. At present effective drugs found are mostly antimony compounds. In the molecules, the state of antimony affects the poison content. The greater the stability of the association, the lower the poisonous content, and the dosage administered can be increased with hopes for the raising of the curative effects.

However, on the other hand, if the stability of antimony compounds is raised too high, while the poisonous effect on the patient will no doubt be reduced, at the same time the capacity for destroying the parasites will also be reduced, and the curative effects will be undermined. Only when we have antimony compounds of a suitable degree of stability may we achieve higher curative indexes.

From results achieved so far, it seems that what meet our demand are: cyclo antimony sulphur alcohol salt of bisulfide compounds with carboxyl; and oxidized aromatic phenyl stibine compounds. If we can discover in our studies some laws governing the relationship between the degree of stability of antimony compounds and curative values, it will be important in guiding the designing of the structure of new drugs.

In China we have already found many new antimony agents which can be used for clinical tests. Though the drugs are different, the antimony component is the same in all of them. Though there may be a difference in the degree of stability, it is still unavoidable that antimony produces its typical secondary effects. There is still no evidence on the resistance capacity of schistosomiasis worms to antimony, but antimony compounds are much less effective when applied to patients suffering a relapse compared with new patients undergoing treatment for the first time. For this reason, it is important that we seek non-antimony compounds.

Hopes are not bright for clinical tests with the drugs reported from outside China, namely: hetero sulphide anthracine ketones; and diamino diphenyl oxide alkyl. As to what we have found in China, rosaniline and hexachlorophene, though their curative values are not yet ideal, nevertheless it is worthy of efforts in making them possibilities in the designing of new drugs, to produce relevant compounds to raise their curative effects.

In addition to the compound drugs, among Chinese traditional drugs, pumpkin seeds can greatly improve the conditions of sufferers from schistosomiasis.(25) But the amount needed for a dose is too large, and it leads to indigestion, while its capacity for destroying the worms is not as pronounced as antimony agents. Hemerocallis flava root has the definite capacity to destroy both grown and small worms, but the poisonous content is too high for clinical application. If we can clarify ourselves on the effective components of these two drugs and proceed further to study the relationship between their chemical structure and pharmaceutical properties, we shall open a new road to the study of new compound drugs.

Notes:

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